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UK Paediatric Oncology *Pneumocystis jirovecii* Pneumonia (PJP) Surveillance Study

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ABSTRACT

Background:

Pneumocystis jirovecii Pneumonia (PJP) is a serious infective complication of immunosuppressive therapy. There are insufficient data concerning the incidence or mortality rate in children undergoing treatment for malignancies and how these may be influenced by prophylaxis.

Objective:

Prospective collection of clinical information for all suspected and proven cases of PJP in children with cancer in the UK and Ireland.

Design:

A surveillance survey was undertaken using a key contact at each paediatric oncology Principle Treatment Centre (PTC).

Main Outcome Measures:

To describe the mortality, outcomes and use of prophylaxis in this at-risk group.

Results:

The study confirms that PJP is rare, with only 32 cases detected in the UK over a 2-year period reported from all 20 PTCs. No deaths were directly attributed to PJP, in contrast to previously reported high mortality rates. Breakthrough infection may occur despite prescription of ostensibly adequate

prophylaxis with co-trimoxazole ~~may occur~~; 11 such cases were identified. Six infections occurred in patients for whom prophylaxis was not thought to be indicated. Two infections occurred in patients for whom prophylaxis was specifically omitted due to concerns about potential bone marrow suppression or delayed engraftment.

Conclusion:

PJP in children treated for malignant disease is rare. Breakthrough infection despite prophylaxis with co-trimoxazole may represent pathogen resistance or non-compliance. Further consideration of the use of PJP prophylaxis during Acute Myeloid Leukaemia and non-Hodgkins Lymphoma treatment is warranted, alongside appraisal of the clinical implications of the possible marrow suppressive effects of co-trimoxazole and its interactions with methotrexate.

BACKGROUND

Pneumocystis jirovecii is an opportunistic parasite that causes pneumonia (PJP) in severely immunocompromised hosts. The incidence of PJP among HIV negative patients is increasing, perhaps due to more intense and diverse immunosuppressive therapies for malignancy, bone marrow and solid organ transplants and rheumatological disease.[1] Even with prompt treatment, PJP has historically resulted in high mortality rates of 20-60%.[2–4] There are insufficient data concerning the incidence or mortality ~~rates~~ in children ~~being~~

treated for malignancies and how these may be influenced by the use of prophylaxis.

After dissemination of a recently designed UK guideline for the prophylaxis of PJP in children with solid malignancies,[5] a survey of compliance and an analysis of PJP cases was undertaken.

METHODS

This was a national surveillance study of suspected or proven PJP over a 2-year period, January 2018 – January 2020 in Children's Cancer and Leukaemia Group (CCLG) networked UK paediatric oncology Principle Treatment Centres (PTCs). Every quarter, centres reported ~~any~~ suspected or proven cases of PJP in the past 3 months with anonymised clinical details (Supporting Information, Appendix 1).

Age and treatment centre were used as identifiers for each case. As PJP is a rare condition this was considered sufficient to identify potential duplicates. All cases of PJP would be expected to come to the attention of the child's PTC, even if that child presented with symptoms to their local hospital as these children's care is highly centralised.

Data were collected regarding the diagnosis of PJP, the underlying malignancy diagnosis and co-morbidities, the stage in anticancer therapy, the total white cell and lymphocyte count at time of presentation with PJP, along with the specific use of prophylaxis in the month prior to PJP, and the clinical outcome.

Proven PJP was defined on the basis of positive respiratory samples, in a clinically relevant setting. Suspected PJP was a clinical diagnosis, based on imaging and response to therapy.

RESULTS

All 20 UK PTCs undertook the surveillance. Thirty-two cases (13 suspected, 19 proven) in 31 patients were identified over the 2-year period. One patient with Acute Lymphocytic Leukaemia (ALL) had a second suspected PJP infection following a microbiologically confirmed infection 6 months previously.

One case was diagnosed on positive immunofluorescence (IF) on samples obtained by bronchoalveolar lavage (BAL). The remaining 18 proven cases were diagnosed by Polymerase Chain Reaction (PCR) on samples from BAL, blood, sputum and/or nasopharyngeal aspirate. Fourteen of the proven cases underwent BAL with positive results (12 PCR positive, 1 IF positive and one IF and PCR positive). No information was recorded regarding suspected cases

who underwent BAL with negative microbiology for PJP. The median age was 9 years 4 months (range 18 months to 18 years).

Of the 20 PTCs, 4 did not report any cases of suspected or proven PJP over the 2-year period but the remainder reported between 1 and 4 cases each. The spread of suspected versus proven cases at the different PTCs was fairly even (see figure 1), suggesting no regional over-reporting or heightened awareness.

Table 1 shows the 32 cases by underlying diagnosis, the most common of which were haematological malignancies (26/31).

Table 1 PJP cases by underlying diagnosis

Underlying Diagnosis	**Number of Cases**	**Detail (further details provided in supporting information)**
Acute lymphoblastic leukaemia	15	10 in maintenance 3 post allogeneic SCT for relapse 1 at initial presentation 1 at presentation with 2nd relapse post allogeneic SCT
Acute myeloid leukaemia	7	2 post allogeneic SCT 3 on MyeChild Protocol
Non-Hodgkins lymphoma	4	All mature B cell NHL treated on FAB-LMB protocols
Neuroblastoma	4	3 post autologous SCT
Alveolar rhabdomyosarcoma	1	
Ewing's sarcoma	1	
Total	**32**	

FAB-LMB, French-American-British-Lymphoma Malins B, NHL, Non-Hodgkins Lymphoma, SCT, Stem Cell Transplant

There were 7 suspected and 8 proven cases of PJP in 14 patients with ALL (1 patient had a proven infection, followed by a suspected infection 6 months later). Of these, 11 cases occurred during maintenance therapy or immediately after the end of treatment, 1 presented at diagnosis and was later found to have an underlying immunodeficiency, 1 at presentation with a second relapse and 2 in the post stem-cell transplant (SCT) phase.

Thirteen of the infections in children with ALL occurred during periods where prophylaxis had been prescribed. Four of these episodes were considered by their clinical team to be consequent to possible or definite non-compliance with prophylaxis. Five cases were apparent prophylaxis failures on oral co-trimoxazole, 2 on oral dapsone, one on intravenous pentamidine and one on nebulised pentamidine. Doses of oral co-trimoxazole were all as per the UKALL 2011 trial protocol, given on 2 days per week.

There were 7 cases of PJP associated with AML (5 proven, 2 suspected). Three were not prescribed any prophylaxis as it was not thought to be indicated. One patient was receiving intravenous pentamidine and the

remaining 3 co-trimoxazole. Only 1 patient was thought to be non-compliant with oral prophylaxis.

There were 3 proven and 1 suspected case of PJP in children with NHL (all mature B cell NHL treated on French-American-British-Lymphoma Malins B (FAB-LMB) protocols). Only 1 had been prescribed prophylaxis (co-trimoxazole) as it was felt to be contraindicated with the frequent use of high-dose (HD) intravenous methotrexate.

The final 6 cases were in 4 patients with neuroblastoma, and 2 in patients with sarcomas. The neuroblastoma patients were treated on the European high-risk neuroblastoma study or CCLG high risk guidelines. Three had received an autologous SCT and one had just completed induction therapy. Only 1 patient was not prescribed any prophylaxis post SCT because of the theoretical delay to count recovery. The last 2 patients had relapsed rhabdomyosarcoma and Ewing's sarcoma with suspected and proven PJP respectively. The former was prescribed co-trimoxazole but thought not to be taking it, and the latter had not been receiving any PJP prophylaxis due to concerns about bone marrow suppression.

At presentation with PJP, the mean white cell count and lymphocyte count was 4.15 x 10^9/litre (range 0-14.8) and 0.44 x 10^9/litre (range 0-1.6) respectively for 29 cases (1 case had no blood test results available and a

further 2 cases were excluded from analysis as their cell counts may have been unreliable at presentation/relapse with leukaemia).

Most patients (64.5%, 20 out of 31) had no co-morbidities other than their underlying malignancy. Only 3 patients had a comorbidity that was identified prior to the diagnosis of their malignancy: obesity, trisomy 21, and premature birth (28 weeks) with a past history of chronic lung disease. None had a known immunodeficiency prior to their diagnosis of cancer but one patient was subsequently found to have mannose binding lectin deficiency.

Gut graft versus host disease (GVHD) has been reported to possibly interfere with oral absorption and efficacy of co-trimoxazole[6] but the only patient reported as having gut GVHD was prescribed intravenous pentamidine.

Twenty-seven patients (84%) made a full recovery, of whom 11 (34% of total) required paediatric intensive care (PICU) admission. There were 3 deaths but none of these were considered directly attributable to PJP.

DISCUSSION

PJP remains a rare complication of treatment for malignancy in paediatric patients. Only 32 cases were identified in all of the UK PTCs over a 2-year period. It is unlikely that any child treated for PJP with an underlying

malignancy was omitted from the study due to the centralisation of UK children's cancer services.

It is remarkably challenging to get good denominator data, but we have attempted to provide an estimate by extrapolating from recent projections of the number of children with cancer treated with systemic anticancer therapy each week UK-wide[7]: *There are approximately 1700 children undergoing chemotherapy each week in the UK, and a similar number may be assumed to receive such treatment each year. We identified 16 cases of PJP per year, giving an estimated incidence rate of 9.4 per 1000 children treated. This is likely to be an overestimate of the true incidence as it is extrapolated from Public Health England data for children aged under 16 years and we included in our study any young person treated by paediatric oncologists, even if they were 16 or older. This may be compared to historical data from the pre-prophylaxis era of 40.8 per 1000 children treated in one US institution over 9 years.* [8]

The number of apparent co-trimoxazole prophylaxis failures was surprising (11 patients), although only prescription, not compliance could be ascertained. Early studies of co-trimoxazole prophylaxis used daily dosing regimens and reported only 1 case of treatment failure.[4,9,10] However, these early studies generally had small numbers of children (80 -229).[9,10] The single case of prophylaxis failure was in a child with ALL included in a prospective open

study of all confirmed cases of PJP in 3314 children treated in one US children's cancer institution over 3 years.[4] It is difficult to directly compare the present data with historical studies as the total number of children given prophylaxis over the time period of surveillance is not known. Furthermore these older studies may be underpowered to detect rare events, such as prophylaxis failure, or over time it is possible that pathogen resistance is emerging.

The optimal dosing schedule for prophylaxis with co-trimoxazole remains to be defined. Subsequent to the first randomised controlled trial of daily co-trimoxazole prophylaxis in children with ALL,[9] studies demonstrated that co-trimoxazole given on 3 days per week is equally effective.[11] More recently other groups have confirmed that cotrimoxazole twice,[12,13] or even once weekly [14] has comparable efficacy. A single case study of once weekly prophylaxis failure in a child undergoing allogeneic SCT was reported last year and was postulated to be due to poor absorption of co-trimoxazole given gastro-intestinal (GI) GVHD.[15] GI GVHD was not reported in any of the prophylaxis failures in the present study.

Only 5 patients were prescribed alternative prophylaxis to co-trimoxazole, either dapsone or pentamidine. These are considered less efficacious than co-trimoxazole [5,16] but were prescribed due to concerns about bone marrow suppression and delayed engraftment.

Six patients with PJP (5 proven, 1 suspected) were not given prophylaxis as it was either not thought to be indicated or was actively contraindicated by either local guidance or trial protocol (3 AML and 3 NHL). A further

2 patients (1 suspected infection with neuroblastoma and 1 proven infection with relapsed Ewing's sarcoma) were not given any form of prophylaxis due to concerns about potential delay in count recovery post SCT, and bone marrow suppression respectively.

In our previously published PJP prophylaxis guideline, [5] we recommended against interrupting prophylaxis with co-trimoxazole for patients receiving autologous SCT unless there is a delay in engraftment (weak recommendation, very low quality evidence). Three studies of low or very low quality [4,12,13] considered the frequency of neutropenia in children taking co-trimoxazole prophylaxis. Reported rates of presumed co-trimoxazole induced neutropenia were only 0.5% to 2%. There exist no studies of the effect of co-trimoxazole prophylaxis on time to neutrophil recovery in children undergoing SCT. However a retrospective case-control study of 17 adult patients showed no difference in time to engraftment following SCT if prophylaxis with co-trimoxazole was interrupted versus given continuously.[17] The benefit of prophylaxis needs therefore to be balanced against a lack of evidence that co-trimoxazole delays engraftment.

Some centres omit co-trimoxazole in patients receiving HD methotrexate as the former is thought to delay the excretion of the latter. At the time of writing our guideline, studies on the effect of concurrent co-trimoxazole on methotrexate administration were of moderate or low quality and gave conflicting results.[18,19] Given the toxicity of delayed methotrexate excretion and the challenges of treating raised methotrexate levels, the guideline development group and peer review agreed that co-trimoxazole should be withheld in patients receiving HD methotrexate. Subsequently a good quality prospective study of methotrexate clearance and toxicity in children with ALL given HD methotrexate and thrice weekly co-trimoxazole has been published.[20] The maximum dose of methotrexate was the same as in the UKALL 2011 trial (5 grams/m^2 over 24 hours) but the dose of co-trimoxazole was greater (75mg/m^2 per dose of trimethoprim component 12 hourly on 3 days per week, opposed to 60mg/m^2 12 hourly given in the UK on 2 days per week). No evidence was found of an interaction between methotrexate and prophylactic co-trimoxazole. In the UK where lower doses of co-trimoxazole are prescribed, it can therefore be assumed safe to continue prophylaxis in those patients receiving HD methotrexate at doses of 5g/m^2 or less. Subsequently the Cancer Research UK Clinical Trials Unit (CRCTU) amended the UKALL2011 trial protocol in May 2018 to recommend that patients should continue co-trimoxazole throughout protocol M and MA.

Of the 3 NHL patients who did not receive any prophylaxis, 2 were on protocols that included methotrexate at doses greater than 5g/m^2 (8- 16g/m^2).

If methotrexate doses are higher than 5g/m^2, it is still prudent to withhold co-trimoxazole, but an alternative prophylaxis agent could be considered.

Children with leukaemia have historically been recognised to be high risk for PJP.[8,9,21,22] An analysis of all children with PJP at a US children's oncology centre between 1962 and 1971 (pre-prophylaxis) reported incidence rates of PJP in 7.7% (41 of 532 children) of ALL and 3.5% (4 out of 113) of AML and monomyelocytic leukaemia patients.[8] Underestimation is probable as diagnosis was established by identification of organisms in material obtained from percutaneous transthoracic needle aspiration of the lung or autopsy. Bronchoscopy with BAL and molecular diagnosis is the current gold standard for diagnosis and is more sensitive.[23] There is a lack of data, subsequent to this publication, on risk for children with AML. The 2016 ECIL (European Conference of Infections in Leukaemia) guidelines for PJP prophylaxis do not recommend routine prophylaxis for children with AML.[16] The Myechild protocol, in agreement with the ECIL guidelines, only recommends PJP prophylaxis for those patients receiving fludarabine.[24] In our study, 3 patients with AML who had not received fludarabine had proven PJP and had not been given any prophylaxis.

Lymphocyte counts alone are considered a poor indication of PJP risk in children treated for malignancies.[5] However we identified only 2 patients at PJP diagnosis with a lymphocyte count above the lower limit of normal (1.5 x

10^9/l) (see figure 2). As data were not collected on patients without PJP, a direct assessment of attributable risk cannot be made, but the finding remains supportive of lymphopenia being a risk factor.

There were no deaths directly attributable to PJP in this surveillance study, in contrast to high published mortality rates of 20-40% in non-HIV patients [4,25–27]. This data is not contemporary and are largely drawn from adult populations. Paediatric studies are historical: the 1973 analysis found a mortality rate of 32% in 41 children with malignancies and PJP treated with intravenous pentamidine.[8] A 1975 study of children with ALL found a mortality rate of 21% for those treated with intravenous pentamidine and 11% for those treated with co-trimoxazole.[21] All the patients in the present study received the current standard treatment: high dose intravenous co-trimoxazole. Pentamidine is less effective as a treatment and other aspects of supportive care have improved in recent years. Due to more sensitive diagnostic methods and improved awareness of PJP risk, diagnosis is probably made more promptly than in the past. Early treatment may contribute to the improved survival in our cohort. Half of the patients in our series made a full recovery without intensive care support.

CONCLUSION

PJP in children treated for malignant disease is rare, with only 32 suspected or confirmed cases detected in the UK over a 2-year period. There were no

deaths directly attributable to PJP, in contrast to previously published high mortality rates. Breakthrough infection despite prescribed prophylaxis with co-trimoxazole may represent pathogen resistance or non-compliance with prophylactic therapy. Six infections occurred in patients for whom prophylaxis was not thought to be indicated and in a further 2 patients for whom no prophylaxis was prescribed due to concerns about toxicity. Further consideration of the use of PJP prophylaxis during AML and NHL treatment is warranted, alongside appraisal of the clinical implications of the possible marrow suppressive effects of co-trimoxazole and its interactions with methotrexate.

Authors' Contributions

Both authors conceived the idea for the study. RP wrote the proposal, approved by BP, for the CCLG and helped establish key contacts in each PTC. RP and BP both worked on the proforma for data collection. RP collected and analysed all the data. Both authors contributed to the final paper.

Ethics Approval and Consent

No patient identifiable data was collected so ethics approval and patient consent were not required.

Data Availability

All data available in supplementary files attached.

Conflict of Interest

The authors declare no conflict of interest

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What is Already Known on This Topic?

PJP is a rare but serious complication of immunosuppressive therapy

Prophylaxis with co-trimoxazole 2 days per week is safe, effective and inexpensive

All children with malignancies undergoing immunosuppressive therapy should be offered prophylaxis unless there are clear contraindications

What this Study Adds

No deaths were directly attributed to PJP, in contrast to previously reported high mortality rates of 20-40%

Breakthrough infection despite prophylaxis with co-trimoxazole is more common compared to previously published data

Further consideration of prophylaxis use during AML and NHL treatment is warranted

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Legends

Table 1 PJP cases by underlying diagnosis

Figure 1 Cases by Principle Treatment Centre

Figure 2 Lymphocyte Counts at Presentation

Supporting Information File

Supporting Information, Appendix 1

ABBREVIATIONS

ALL	Acute Lymphoblastic Leukaemia
AML	Acute Myelocytic Leukaemia
BAL	Bronchoalveolar lavage
BC	Blood culture
BNF	British National Formulary
Bu-Mel	Busulphan & mephalan
CCLG	Children's Cancer and Leukaemia Group
CLD	Chronic lung disease

CMV	Cytomegalovirus
CYVE	Cytarabine & etoposide
Dex	Dexamethasone
FLA-Ida	Fludarabine, cytarabine, idarubicin
FR	Full recovery
GI	Gastrointestinal
GVHD	Graft versus host disease
HD	High Dose
HD-Ara-C	High dose cytarabine
HIV	Human Immunodeficiency Virus
IF	Immunofluorescence
IV	Intravenous
LCH	Langerhans cell histiocytosis
MA	Mitoxantrone & cytarabine
MMF	Mycophenolate mofetil
MTX	Methotrexate
MUD	Matched unrelated donor
NBL	Neuroblastoma

NOPHO	Nordic Society for Paediatric Haematology and Oncology
PCP	*Pneumocystis carinii* Pneumonia
PCR	Polymerase chain reaction
PEG	Pegalated
PICU	Paediatric intensive care unit
PJP	*Pneumocystis jirovecii* Pneumonia
PTC	Primary treatment centre
R-CYM2	Continuous infusion cytarabine & high dose methotrexate
RCT	Randomised Controlled Trial
RMS	Rhabdomyosarcoma
RSV	Respiratory syncytial virus
RT	Radiotherapy
SCT	Stem cell transplant
T21	Trisomy 21
TBI	Total body irradiation
TMP-SMX	Trimethoprim-sulfamethoxazole

TPN	Total parenteral nutrition
VCR	Vincristine
VOD	Veno-occlusive disease
WBC	White blood cell count

Figure 2 Lymphocyte Counts at Presentation

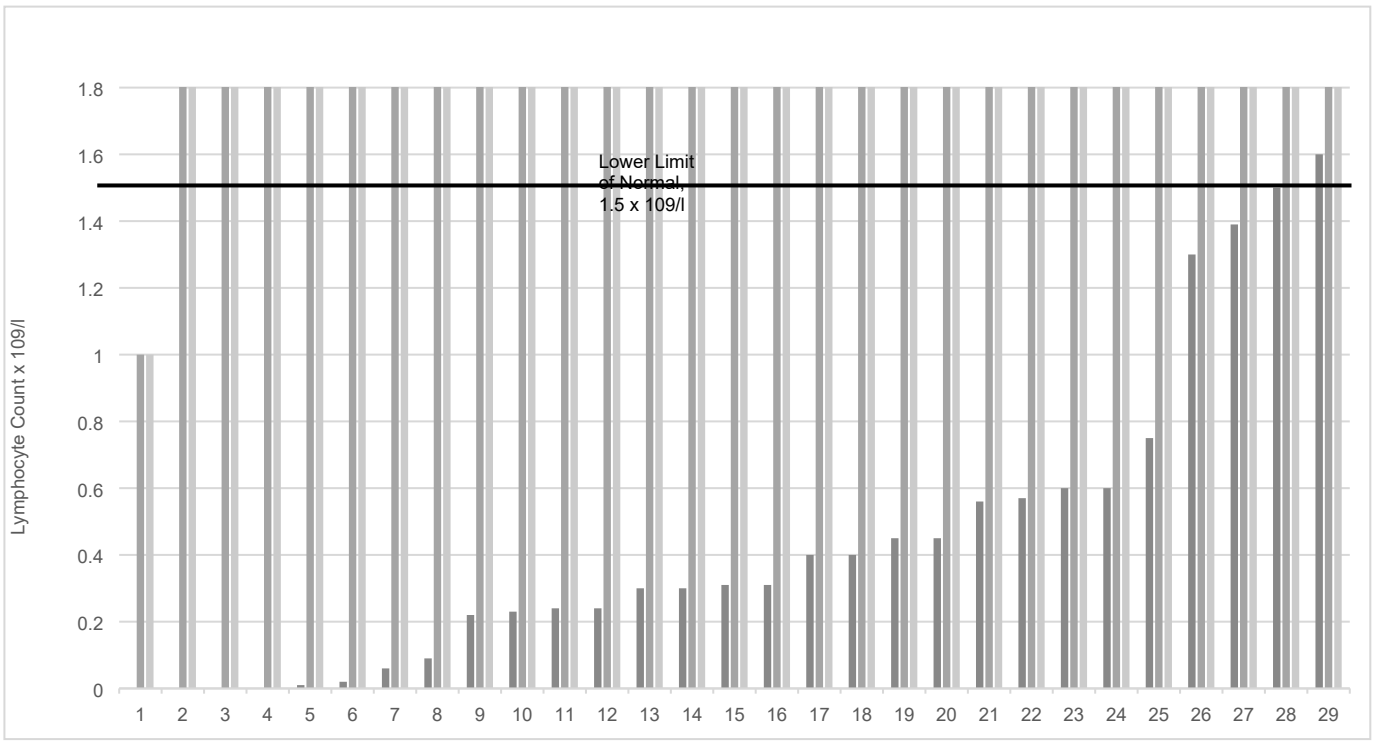

Table 2 Acute Lymphoblastic Leukaemia (ALL) Cases

Age	PJP diagnosis	Co-morbidities	Protocol	WBC	Lymph	Prophylaxis		Outcome
							Receiving & Taking?	
Proven Infections								
3y, 3m	IF on BAL sample	Mannose binding lectin deficiency	At presentation	7.81	1.8	No	n/a	FR
18y, 10m	PCR on BAL sample	None	UKALL 2011 Reg C maintenance	4.37	0.57	TMP-SMX	Unsure	FR
2y, 6m	PCR on BAL sample	Failure to thrive, on TPN	Interfant 06- maintenance	1.1	0	Dapsone	Yes	FR
8y, 11m	PCR on BAL	None	UKALL 2011 Reg C, high risk MRD, had extra therapy including NOPHO A and B, inotuzamab, blinatuzamab and FLA Ida	0.7	0.22	TMP-SMX	No	PICU with FR
17y, 7m	PCR on BAL	Co-incident Aspergillus infection, thought clinically less significant than PJP	UKALL 2011 Reg M maintenance	1.5	0.09	Dapsone	Yes	PICU with FR
3y 11m	PCR on BAL	Co-incident aspergillus and stenotrophomonas in BC, 2nd relapse	Palliation for refractory ALL, over 6m from BMT	1.26	0.31	IV pentamidine	yes	Recovery from PJP, palliation for ALL
4y, 10m	PCR on sputum	Persistently low lymphocyte counts in maintenance of unknown cause	UKALL2011 Reg B maintenance	0.83	0.02	TMP-SMX	yes	PICU with FR
4y, 5m	PCR on BAL	None	UKALL2011 Reg B maintenance	4.19	0.56	TMP-SMX	Yes	FR

Suspected Infections								
18y, 2m	CT chest, Oxgyen requirement, previous PJP, improved with highdose TMP-SMX	Previous PJP, weight loss	A few weeks off treatment, (UKALL2011 Regimen B stopped early because of weight loss and transfusion needs)	11.6	1.5	Nebulised Pentamidine	yes	FR
10y, 4m	CXR, CT, response to therapy	None	UKALL 2011 reg C maintenance	7.2	0.45	TMP-SMX	Yes	PICU with FR
14y, 6m	CXR, CT, response to therapy	Obesity, endocarditis	UKALL 2011 Reg C maintenance	0.58	0.24	TMP-SMX	Yes	Death more likely from other causes
13y, 11m	CT, response to therapy, profound hypoxia on exertion	None	UKALL 2011 Reg C maintenance	3.3	0.24	TMP-SMX	unsure	FR
10y, 9m	CXR, CT	2nd relapse	At presentation with relapse	17.9	12.53	no	n/a	Death more likely from other causes
18y, 4m	CXR, response to therapy	None	UKALL 2011 maintenance	4	0.3	TMP-SMX	no	FR
10y, 4m	CXR, CT, response to therapy	Mild skin GVHD, CMV infection, relapsed ALL	Day 22 post SCT (cyclophosphamide/TBI)	9.9	0.3	TMP-SMX	Yes	FR

Table 3 Acute Myeloid Leukaemia (AML) cases

Age	PJP diagnosis	Co-morbidities	Protocol	WBC	Lymph	Prophylaxis		Outcome
				x10^9/l			Receiving & Taking?	
Proven Infections								
9y, 9m	PCR on BAL, CT chest	None	AML guidelines, following cycle 3, HD-Ara-C	0.06	-	None	-	FR
12y, 7m	PCR on induced sputum	On treatment for TB meningo-encephalitis	10m post 2nd MUD HSCT, on ciclosporin & MMF for GVHD prophylaxis	12.4	0.4	TMP-SMX	no	PICU with FR
6y, 7m	IF and PCR on BAL, CT chest, response to therapy	None	Myechild, post course 2 MA	8.73	1.39	None	-	FR
14y, 4m	PCR on BAL	None	MyeChild 01, post cycle 1 (one dose of gemtuzumab with MA) day 22	1.6	1.6	none	-	PICU with FR
11y, 7m	PCR on BAL, CT chest	None	MyeChild 01, post cycle 2 – FLA-Ida day 43	0.1	-	TMP-SMX	Yes	AML disease progression, ongoing O2 requirement, palliative care
Suspected Infections								
15y, 8m	CXR, response to therapy	None	Post FLA	0.1	0	TMP-SMX	yes	FR
2y, 2m	CXR, CT chest	T21, RSV bronchiolitis, bocca virus, GVHD skin/gut, VOD	Day 39 post HSCT. Reduced intensity pretransplant conditioning with busulfan and fludarabine	14.8	1.3	IV pentamidine	yes	Death more likely due to other causes

Table 4 Non-Hodgkin's Lymphoma (NHL) Cases

Age	PJP diagnosis	Co-morbidities	Protocol	WBC	Lymph	Prophylaxis		Outcome
							Receiving & Taking?	
Proven Infections								
6y, 8m	PCR from NPA & blood	None	Inter-rituximab study, Group C, completed induction and consolidation, due to start maintenance	<0.1	0.01	no	No	FR
14y, 11m	PCR on BAL	None	Inter B 2010 with rituximab, stopped post CYVE 1 due to toxicity	4.9	0.06	TMP-SMX	yes	PICU with FR
3y, 7m	PCR on NPA	None	Inter-BNHL Group B with rituximab R-CYM2 day 21	Unknown	Unknown	No	No	FR
Suspected Infections								
5y, 2m	CXR, CT, lower than expected O2 sats	Ex-prematurity, 28 weeks, CLD resolved by 18m	Group C- CYVE 2 day 10	3.2	0.23	No	No	FR

Table 5 Neuroblastoma Cases

Age	PJP diagnosis	Co-morbidities	Protocol	WBC	Lymph	Prophylaxis		Outcome
							Receiving & Taking?	
Proven Infections								
1y, 6m	PCR on sputum and NPA	None	European HR neuroblastoma study, 1st cycle cis-retinoic acid post autologous SCT	6.5	0.45	TMP-SMX	Yes	PICU with FR
2y 2m	PCR on BAL sample	None	CCLG guidelines for HR neuroblastoma. Post-surgical resection	5.8	0.31	TMP-SMX	Yes	PICU with FR
Suspected Infections								
3y, 3m	CXR, CT	Previous suspected fungal pneumonitis	European HR neuroblastoma study, Day 38 post autologous SCT (BuMel conditioning)	2.4	0.6	no	n/a	FR
2y, 9m	CXR	None	European HR neuroblastoma study, Day 35 post autologous SCT (BuMel conditioning)	3.4	0.6	TMP-SMX	Yes	PICU with FR

Table 6 Rhabdomyosarcoma

Age	PJP diagnosis	Co-morbidities	Protocol	WBC	Lymph	Prophylaxis		Outcome
							Receiving & Taking?	
6y, 11m	CXR, clinical symptoms	Relapsed alveolar rhabdomyosarcoma	Metronomic oral antiangiogenesis regimen: celecoxib, thalidomide, and fenofibrate, with alternating 21-day cycles of low-dose cyclophosphamide and etoposide & palliative radiotherapy to spine	2.09	0.75	TMP-SMX	No	PICU with FR

Table 7 Ewing's sarcoma

Age	PJP diagnosis	Co-morbidities	Protocol	WBC	Lymph	Prophylaxis		Outcome
							Receiving & Taking?	
17y	PCR on BAL	Relapsed Ewing's with chest disease, thoracotomy. QTc prolongation, impaired renal function, moderate hearing loss, peripheral neuropathy, Vit B12 and folic acid deficiency with some GI intolerance	On oral Etoposide following wedge resection	3.9	0.4	no	n/a	PICU with FR

Table 8 No Prophylaxis Prescribed

Underlying Diagnosis	PJP diagnosis	Protocol	Reason for no prophylaxis
ALL	proven	At diagnosis	At diagnosis
Relapsed ALL	suspected	At relapse	At relapse
AML	proven	AML guidelines, following cycle 3, HD-Ara-C	Not routinely prescribed for AML at this PTC
AML	proven	Myechild, post course 2 MA	Not indicated by Myechild protocol
AML	proven	MyeChild 01, post cycle 1 (one dose of gemtuzumab with MA) day 22	Not indicated by Myechild protocol
NHL	proven	Inter-rituximab study, Group C, completed induction and consolidation, due to start maintenance	Not thought indicated
NHL	suspected	Group C- CYVE 2 day 10	Not thought indicated
NHL	proven	Inter-BNHL Group B with rituximab R-CYM2 day 21	Not thought indicated
Neuroblastoma	suspected	European HR neuroblastoma study, Day 38 post autologous SCT (BuMel conditioning)	Not given post SCT because of theoretical delay to count recovery
Relapsed Ewing's	proven	On oral Etoposide following wedge resection	Concerns regarding bone marrow suppression given past episodes of severe febrile neutropaenia

Table 9 Co-trimoxazole prophylaxis failure (non-compliance not confirmed)

Underlying Diagnosis	Age	PJP Diagnosis	Protocol	Outcome
ALL	10y, 4m	Suspected	UKALL 2011 Reg C maintenance	PICU with FR
ALL	14y, 6m	Suspected	UKALL 2011 Reg C maintenance	Death more likely from other causes
Relapsed ALL	10ym 4m	Suspected	Day 22 post SCT (cyclophosphamide/TBI)	FR
ALL	4y, 10m	Proven	UKALL 2011 Reg B maintenance	PICU with FR
ALL	4y, 5m	Proven	UKALL 2011 Reg B maintenance	FR
Neuroblastoma	2y, 9m	Suspected	European HR neuroblastoma study, Day 35 post autologous SCT (BuMel conditioning)	PICU with FR
Neuroblastoma	2y 2m	Proven	Post surgical resection	PICU with FR
Neuroblastoma	1y, 6m	Proven	European HR neuroblastoma study, 1st cycle cis-retinoic acid post autologous SCT	PICU with FR
AML	15y, 8m	Suspected	Post FLA	FR
AML	11y, 7m	Proven	MyeChild 01, post cycle 2 – FLA-Ida day 43	AML disease progression, ongoing O2 requirement, palliative care
NHL	14y, 11m	Proven	Inter B 2010 with rituximab, stopped post CYVE 1 due to toxicity	PICU with FR

Table 10: Age, Non-compliance and Prophylaxis Failure

		Range
Mean Average Age of all 32 Presentations	9 years and 3 months	18 months to 18 year and 10 months
Median Age of all 32 Presentations	9 years and 4 months	
Average Age of Non-compliant Patients (N=5)	14 years and 6 months	8 years 11 months to 18 years 10 months
Average Age of Remaining 27 Presentations	9 years and 3 months	18 months to 18 years and 2 months
Average age of co-trimoxazole failures (N=11)	8 years and 5 months	18 months to 15 years and 8 months

Abbreviations

ALL	Acute Lymphoblastic Leukaemia
AML	Acute Myelocytic Leukaemia
BAL	Bronchoalveolar lavage
BC	Blood culture
BNF	British National Formulary
Bu-Mel	Busulphan & mephalan
CCLG	Children's Cancer and Leukaemia Group
CLD	Chronic lung disease
CMV	Cytomegalovirus
CYVE	Cytarabine & etoposide
Dex	Dexamethasone
FLA-Ida	Fludarabine, cytarabine, idarubicin

FR	Full recovery
GI	Gastrointestinal
GVHD	Graft versus host disease
HD	High Dose
HD-Ara-C	High dose cytarabine
HIV	Human Immunodeficiency Virus
IF	Immunofluorescence
IV	Intravenous
LCH	Langerhans cell histiocytosis
MA	Mitoxantrone & cytarabine
MMF	Mycophenolate mofetil
MTX	Methotrexate
MUD	Matched unrelated donor
NBL	Neuroblastoma
NOPHO	Nordic Society for Paediatric Haematology and Oncology
PCP	*Pneumocystis carinii* Pneumonia
PCR	Polymerase chain reaction
PEG	Pegalated
PICU	Paediatric intensive care unit
PJP	*Pneumocystis jirovecii* Pneumonia
PTC	Primary treatment centre
R-CYM2	Continuous infusion cytarabine & high dose methotrexate
RCT	Randomised Controlled Trial
RMS	Rhabdomyosarcoma
RSV	Respiratory syncytial virus

RT	Radiotherapy
SCT	Stem cell transplant
T21	Trisomy 21
TBI	Total body irradiation
TMP-SMX	Trimethoprim-sulfamethoxazole
TPN	Total parenteral nutrition
VCR	Vincristine
VOD	Veno-occlusive disease
WBC	White blood cell count

Pneumocystis jirovecii Pneumonia (PJP) Surveillance Questionnaire

Please complete if you have seen a patient with suspected or proven PJP
(previously known as *Pneumocystis carinii* Pneumonia, PCP) in the last 3 months:

1. Age in years and months	
2. Primary Treatment Centre	
3. Suspected or proven diagnosis of PJP?	
4. If suspected, was this on the basis of: (tick all that apply)	i. ☐ CXR appearance ii. ☐ CT chest appearance iii. ☐ Response to therapy iv. ☐ Other – please specify:
5. If proven, what positive samples were obtained?	
6. Underlying malignant diagnosis	
7. Other relevant co-morbidities (e.g. immunodeficiency, bronchiectasis):	
8. Treatment Protocol/Trial and place in protocol (e.g. Wk145 maintenance, D+45 BuMel HSCT, 3 weeks after EoT)	
9. White cell count & lymphocyte count at presentation with recognised PJP:	
10. Was the patient prescribed PJP prophylaxis in the month prior to PJP diagnosis?	1. ☐ Yes : Go to Q 11, 12 & 14 2. ☐ No : Go to Q 13 & 14 3. ☐ Unsure : Go to Q 14
11. What form of prophylaxis was prescribed (tick all that may apply)?	a. ☐ Enteral co-trimoxazole *Please specify dose/regimen in comments underneath (for example as per UKALL2011, 2 days per week*)* b. ☐ Parenteral co-trimoxazole c. ☐ Nebulised pentamidine d. ☐ Intravenous pentamidine e. ☐ Dapsone f. ☐ Atovaquone

PJP Surveillance Study, Chief Investigator Dr Rebecca Proudfoot, Rebecca.proudfoot1@nhs.net

	g. ☐ Other – please specify h. ☐ Unknown Comments:
12. Do you believe the patient was receiving and taking the prescribed prophylaxis in the month prior to diagnosis? (skip to Q14)	a. ☐ Yes b. ☐ No c. ☐ Unsure
13. Please tick all the reasons that apply as why prophylaxis was not prescribed:	a. ☐ Not thought to be indicated by physician b. ☐ Parental or patient active choice c. ☐ Error (i.e. not considered by medical team) d. ☐ Allergy/ intolerance – please specify to which drug e. ☐ Other – please specify:
14. Clinical outcome (please tick all that apply):	a. ☐ Full recovery b. ☐ PICU admission with recovery c. ☐ Death probably attributable to PJP d. ☐ Death more likely attributable to other causes e. ☐ Unknown f. ☐ Not yet established

Any Further Comments:

*Co-trimoxazole dosing as per UKALL2011

Drug	Surface Area	Dose	Route	Frequency
Co-trimoxazole	<0.5m^2	24mg/kg	oral	Twice Daily on 2 consecutive days per week
	0.5-0.75m^2	240mg		
	0.76-1m^2	360mg		
	>1m^2	480mg		